of lactic acid (presence of lactic acid, 78 per cent. positive Wolff-Junghans test 83 per cent.), or the Oppler-Boas bacilli (presence of Oppler-Boas bacilli, 76 per cent. positive Wolff-Junghans test, 83 per cent.).

A positive reaction rarely occurs in malignant growths in the abdomen not involving the stomach; in gastric ulcer, except in cases associated with stenosis and dilatation or in chronic gastritis or simple achylias. While the test is of value as an aid in the diagnosis of gastric carcinoma, it is only then of significance when taken in connection with the other signs of the disease, and thus is an additional means of aiding in the detection of a disease frequently most difficult of diagnosis.

THE PHARMACOLOGY OF EMETIN.

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In recent years a considerable amount of interest has been attached to the alkaloid emetin. This has been due in the first place to the striking results obtained with it in the treatment of amebic dysentery, and secondly to its present wide-spread use in pyorrhea alveolaris. In connection with its use in dysentery it is interesting to note in the fifth edition of Cushny's *Pharmacology*, 1910, that while ipecacuanha is accepted as being almost a specific, doubt is cast on the part played by emetin, and in fact, mention is made of a "de-emetinized" ipecac said to act equally well. Meyer and Gottlieb in their *Experimental Pharmacology*, second edition, 1911, state that the effective factor is the tannic acid contained in ipecac. The careful work of Rogers,[1] however, has established definitely that the curative effects of ipecac are due entirely to the emetin it contains, and that emetin may rightfully be classed as a specific for the amebic type of dysentery.

The use of emetin in pyorrhea alveolaris is of much more recent origin and is due especially to the work of Bass and Johns,[2] who have

[1] British Med. Jour., 1912, No. 1, 1424; 1912, No. 2, p. 405; Dysenteries, Oxford University Press, 1913.

[2] New Orleans Med. and Surg. Jour., 1914, lxvii, 456; Jour. Am. Med. Assn., 1915, lxiv, 553; Alveolodental Pyorrhea, Philadelphia and London, Saunders Co., 1915.

assumed that the Entamoeba buccalis is an important factor in this disease, and is affected by emetin in the same specific manner as the Amoeba histolytica. Following their publications and those of Smith and Barrett[3] and others, emetin has achieved a new prominence, and has become very extensively employed in the treatment of pyorrheal infections. In this at-present popular use of the drug, scant attention is paid to other and deleterious actions it may possess, and it is not at all improbable in view of the somewhat unusual toxic effects it may induce in animals, that considerable damage has already been done through injudicious dosage or too long-continued administration. For this reason it seems desirable to examine into the pharmacology of emetin, to confirm observations already brought out by experimental means, and to add such additional facts as may seem of importance.

The literature on the pharmacology and clinical effects of emetin is fairly extensive, but contains comparatively few publications based on careful experimental work. In the earlier work the preparation used was not pure emetin, but a mixture of emetin and cephaelin. The two alkaloids are closely related chemically, however, and their actions in general are the same, the chief differences being that cephaelin is more irritant locally, more apt to damage the kidney, and less toxic to the heart. This has been made clear by the work of Lowin,[4] who obtained the two alkaloids in pure form. His experimental results with pure emetin differ in no appreciable degree from those of earlier investigators, notably Podwyssotzki,[5] so that it is safe to assume that the latter made use of a mixture in which the emetin action was the predominant one.

The main toxic effects of emetin, as shown by practically all of the earlier workers, are exercised on the gastro-intestinal tract and on the heart. Magendie and Pelletier,[6] in 1817, demonstrated that the emetic action of ipecac was due to its alkaloid content, and further that the alkaloid, regardless of whether given by mouth or injection, produced a definite inflammatory reaction along the mucous membrane of the alimentary tract. Duckworth,[7] in 1871, found that toxic doses caused a cardiac paralysis which came on suddenly and quickly caused death of the animal. Doses not large enough to induce cardiac paralysis, produced no changes in the circulation. Other investigators have elaborated on these actions and have added further ones.

The local irritant action of emetin has been long recognized. Duckworth mentions that apothecaries in pulverizing ipecac root are very apt to have marked irritation of the conjuctiva and nasal

[3] Jour. Amer. Med. Assn., 1914, lxiii, 1746; Dental Cosmos, 1914, lvi, 948.
[4] Arch. Internat. de Pharmacod., 1902, xi, 9.
[5] Arch. f. exper. Path. u. Pharmakol., 1879, xi, 231.
[6] Jour. de Pharmacie, 1817, iii (quoted by Podwyssotzki).
[7] St. Bartholomew's Hosp. Reports, 1869, v, 1218; and 1871, vii, 91.

mucous membrane. Lowin found that a 1 to 500 solution of emetin applied to the conjunctival sac produced a violent irritation. He states, however, that an irritation of subcutaneous tissues following injection does not occur, and concludes from his experiments that emetin is a specific irritant to mucous membranes. The emesis produced by emetin has been generally considered as an expression of the irritation of the gastric mucous membrane. Subcutaneous injection, it is true, causes emesis, but the dose necessary is not smaller than that given by oral administration, nor is the time required for vomiting to occur noticeably shorter. Foulkrod[8] claims to have found emetin in the stomach after subcutaneous injections, and looks on this as additional evidence of the peripheral action in emetin emesis. Hatcher and Eggleston,[9] on the other hand, have recently reported experiments in which emetin caused definite vomiting movements and symptoms of nausea in animals whose stomachs had been completely removed. They conclude, therefore, that the emetic action is due in great part, if not entirely, to action on the vomiting centre.

The changes induced in the intestinal tract, which come in from 18 to 24 hours after administration of emetin, may be summarized as follows: The mucosa of the small intestine and, to a less extent, that of the large intestine may be only slightly injected, with a catarrhal swelling, or the whole surface may be of a dark red color, and covered with a dry mucopurulent secretion. Sometimes the general reddening is absent and there are seen hyperemic areas covered with a yellowish exudation. Numerous sharp walled round ulcers are occasionly seen.

On the circulation, the paralyzing effect of emetin on the heart muscle, described by Duckworth, has been confirmed by later workers. Podwyssotzki[10] has shown in the frog's heart that an irregularity of rhythm develops early, both auricle and ventricle beating more slowly, but the ventricular slowing being more marked than the auricular. The auricle may contract twice to a single ventricular contraction, but soon the difference becomes greater, and the auricle may have many contractions to one of the ventricle. Eventually both auricle and ventricle stop in diastole, and are no longer able to respond to stimulation. In mammals, moderate doses caused a sharp fall in blood-pressure, with a quick recovery. With fatal doses the blood-pressure sinks to zero in a few seconds with an accompanying stoppage of the heart.

The action on the central nervous system has also been carefully examined by Podwyssotzki. In the frog, there is a general paralysis coming on in from $\frac{1}{2}$ to $1\frac{1}{2}$ hours. This begins with a depression of voluntary movements, with no changes in reflex activity. Later

[8] Phila. Med. Times, 1878, viii, 554.
[9] Jour. Pharmacol. and Exper. Therap., 1915, vii, 233.
[10] Loc. cit.

the reflexes disappear, while the voluntary muscle and motor nerves remain unaffected. According to this work, therefore, the drug produces a slowly descending central paralysis. Podwyssotzki was unable to detect a toxic effect on either voluntary muscle or motor nerve, although Kobert[11] later found that if the dose be large, a definite impairment of muscular function occurs.

The action on the respiratory tract is one of especial interest, since ipecac has been so largely used as an expectorant and also to check pulmonary hemorrhage. Magendie and Pelletier found in animals killed by emetin an inflammatory condition of the lungs. Duckworth found the lungs hemorrhagic and edematous, and the bronchi strongly injected. Podwyssotzki also found edema and marked irritation, but not in all of his experiments, and states that the pulmonary action is not a constant one. In a study on a series of patients with pulmonary disease given emetin, Zepf[12] was unable to observe any increase in amount or fluidity of bronchial expectoration. In two of the cases hemoptysis developed. This latter result together with the liability to cause vomiting brought Zepf to the conclusion that emetin is actually contra-indicated in pulmonary hemorrhage.

Of other organs acted on, the kidney undergoes some damage according to Foulkrod, who found albuminuria in animals given emetin. Zepf also found small amounts of albumin in most of the cases referred to above. No account is given of changes in the liver except a statement by Foulkrod that the sugar content is less than normal.

The changes in metabolism under emetin, have been studied by Meyer and Williams.[13] They found that emetin brings about a decrease in the carbon dioxide content of the blood, the oxygen content remaining unchanged. This effect, which is considered as one due to acidosis, they believe to result from an inhibition of cellular oxidation processes.

There remains the question of excretion of emetin. Some of the earlier experimenters state that the drug can be detected in the stomach after subcutaneous injection. Foulkrod states that it is excreted unchanged in part through the kidney, in part through the mucous membrane of the stomach and intestine. The methods used, however, are such as to invalidate these findings. Podwyssotzki and also Lowin were unable to detect the drug in any of the excretions.

In our own experiments, we have first noted the cause of death in emetin poisoning.[14] There are three types of this,

[11] Therap. Monatsh., 1902, xvi, 387.
[12] Arch. internat. de Pharmacod., 1904, xii, 345.
[13] Arch. f. exper. Path. u. Pharmakol., 1881, xiii, 70.
[14] The emetin used in these experiments was obtained from Hoffmann-La Roche Chemical Works, Inc., who guaranteed its purity.

dependent on the dose and manner of administration. Death occurs most promptly following intravenous administration and is due to cardiac paralysis. If a sufficiently large dose be given by subcutaneous injection (in cats 0.15 gm. per kilogram weight) death occurs usually in about 4 hours, and is due to respiratory failure. The heart is also affected and this is a contributory factor. With smaller doses death occurs in from 18 to 36 hours, and is due primarily to gastro-intestinal changes.

It is only in the last type of poisoning, that is, where death does not occur until after 18 hours, that definite postmortem changes are found.

With large doses of emetin, the chief site of lesion is the gastro-intestinal tract. The mucosa is highly injected and hemorrhagic, and is covered with bile-stained secretion. There may also be seen small areas of ulcerations. This condition is evident along the entire gastro-intestinal tract.

It is only with large doses that changes other than congestion may be seen in the liver and these consist only of a few scattered areas of focal necrosis. The lungs usually appear emphysematous and anemic with a slight amount of edema. The bronchi are hyperemic. The heart, kidneys, and other organs show evidences of congestion only.

If smaller doses are given so that the animal may survive for 3 or 4 days, the reactions are not so marked and have a tendency for selective location. In these cases the mucosa of the stomach is rarely affected. The duodenum and the upper part of the jejunum show the characteristic changes, which diminish in intensity downward, the lower part of the small intestine often appearing normal. The cecum and large intestine take on the hemorrhagic appearance that is seen in the upper part of the tract.

From the changes induced in the gastro-intestinal tract, it is safe to assume even in the absence of chemical tests, that emetin is excreted in greatest amounts by the stomach and intestines. It would seem also that the excretion is chiefly through the upper part of the small intestine, since with smaller doses this is the part most strongly affected. In respect to this excretion, emetin may be classed with colchicin, diphtheria toxin, the heavy metals and many other drugs[15] which produce similar gastro-intestinal changes.

In studying the effects of emetin on the circulation we determined first those which were shown by blood-pressure variations. In a medium sized anesthetized dog, the intravenous injection of 0.01 gm. of emetin hydrochloride causes a very temporary and hardly noticeable rise in blood-pressure which is followed by a sharp fall. The pressure then rather quickly rises to the normal level or to a point slightly above normal. The fall in pressure, which is the char-

[15] Heubner, Arch. f. exper. Path. u. Pharmakol., 1907, lvi, 370.

acteristic change, averages about 40 mm. Hg. when the initial pressure is about 150 mm. Hg., that is, the fall is approximately 25 per cent. The whole cycle of change takes place in from 2 to 2½ minutes as a rule (Fig. 1). Some exceptions to these statements may be noted in that the fall in pressure may not be as marked, the recovery less rapid, and the subsequent rise above normal more prolonged.

With larger doses, up to 0.04 gm., the blood-pressure changes are similar but the fall is more marked. It is not, however, definitely proportional to the dose. After the initial injection subsequent ones of the same amount produce successively increasing effects, that is, both the actual and percental fall becomes greater. In some

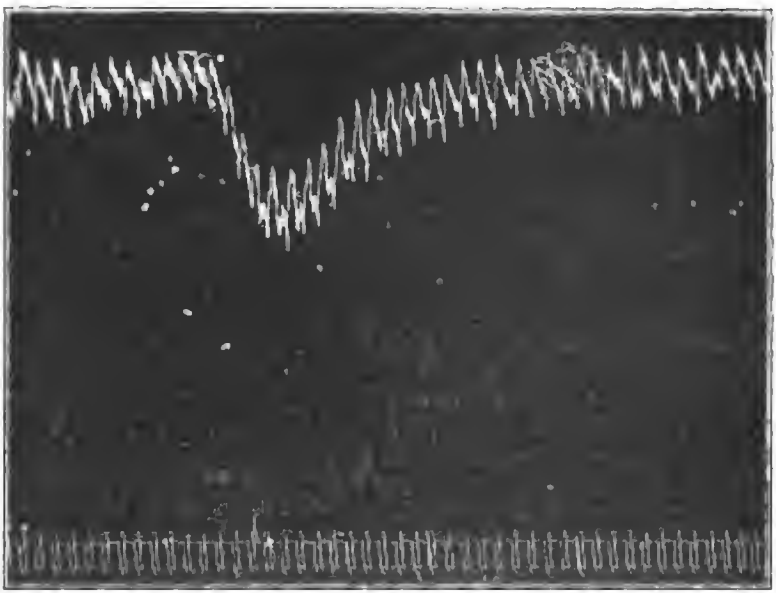

FIG. 1.—Carotid blood-pressure in a dog, showing the fall and recovery following an intravenous injection of 10 mgs. emetin hydrochloride.

instances after 0.04 gm., and as a rule after doses above this, recovery fails to occur after the drop in pressure. The pressure continues to fall gradually until the zero line is reached when death occurs. With the low pressure the heart rate is markedly decreased.

Volumetric changes in different organs have been studied in relationship to the blood-pressure changes described. The volume of the kidney, loop of intestine, and the leg decreases simultaneously with the fall in pressure (Fig. 2). It follows, therefore, that the fall in blood-pressure is not due to a dilatation of bloodvessels, but must be ascribed entirely to a cardiac weakness. This is what the earlier workers on emetin have assumed.

In studying more directly the effect of the drug on the heart we

have confirmed the results obtained by Podwyssotzki and Lowin in the frog's heart. The application of a few drops of a 1 per cent. emetin solution to an exposed frog's heart induces a typical picture of heart block. There is first noted a progressive slowing in the rate

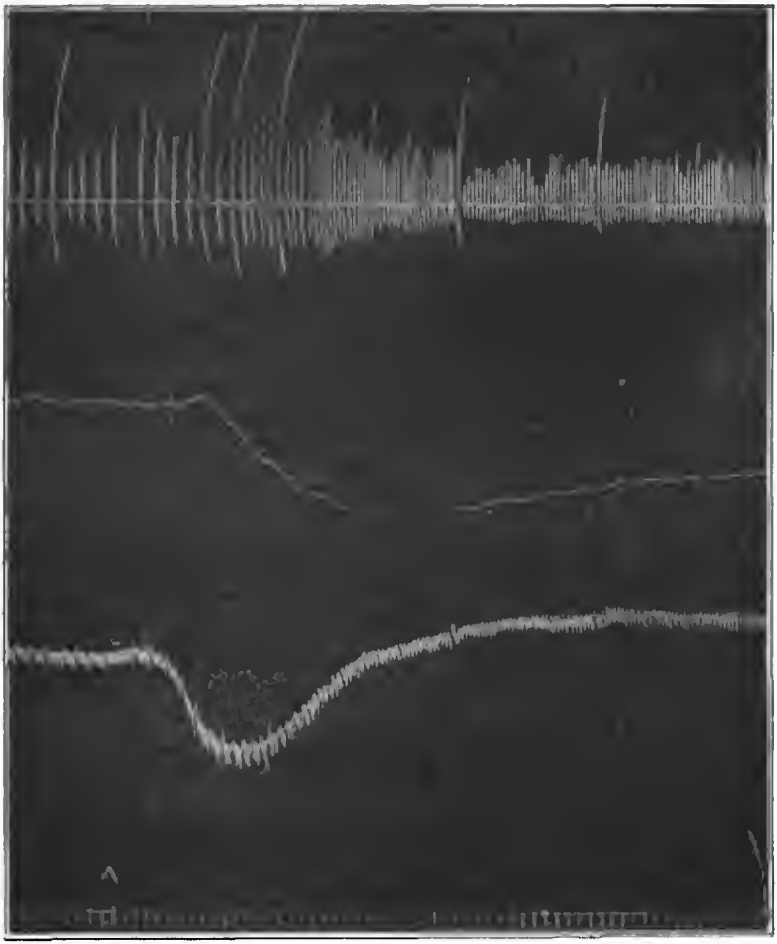

FIG. 2.—Record of respiratory movements (upper), intestinal volume (middle), and carotid blood-pressure (lower) in dog. Time marker registers three second intervals. At *A*, 20 mgs. emetin hydrochloride was injected intravenously. Coincident with the fall in pressure the intestinal volume lessens while the respiratory movements become increased.

of contraction of both auricle and ventricle. Later an occasional dropping out of a ventricular beat occurs, and then a complete dissociation, the auricular-ventricular rhythm being 2 to 1, then 3 to 1, 5 to 1, etc. Finally the ventricle contractions stop, the

auricle beating for a considerable time longer. The turtle's heart behaves in a similar manner (Fig. 3).

The record of the contractions of the mammalian heart, taken with a Cushny myocardiograph, fails to show a dissociation of auricle and ventricle. In the dog, following an intravenous injection of 0.04 gm., the auricle shows a marked weakening in contraction, the ventricle a lessened contraction and an increased relaxation as well (Fig. 4). These changes occur synchronously with the fall in blood-pressure, and the decrease in volume of organs tested. With larger doses the effect is intensified, and the heart contractions cease. The auricular contractions stop some time before those of the ventricle.

The cardiac weakening and fall in blood-pressure are not influenced by either cutting the vagi or administration of atropin. The action, therefore, is on the heart muscle and not on the vagus. An improvement occurs after both epinephrin and strophanthin, but

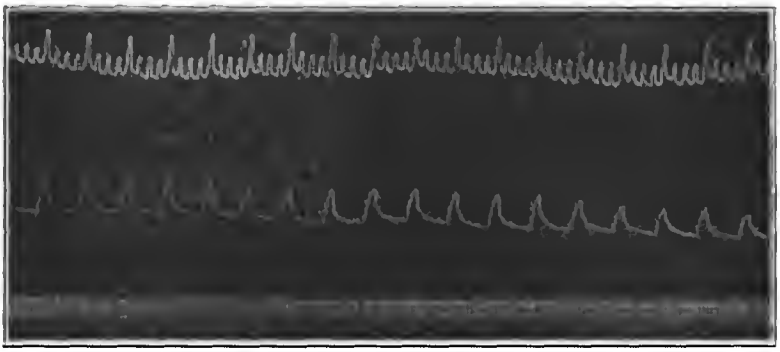

FIG. 3.—Record of contractions of turtle's heart perfused with Locke's solution, to which emetin hydrochloride has been added. The upper record shows auricular contractions, the lower, ventricular. Time marker registers one-second intervals. The auricular-ventricular rhythm is 4 to 1.

this is temporary, and delays only for a short time the complete cardiac paralysis. The myocardiographic tracing is identical with that obtained with chloroform or other cardiac depressants.[16]

We have repeated and confirmed the work of others on the action on the central nervous system. In the frog the action is that of a slowly descending paralysis. At a time when this is complete, with abolition of all reflex activity, both motor nerve and muscle respond to stimulation in a normal manner. The injection of a dose of 0.005 gm. of emetin into the dorsal lymph sac, which is sufficient to produce these effects, brings on a cardiac paralysis in the frog which becomes complete before the central nervous paralysis.

[16] We have noted a fact here worth calling attention to. In one experiment, in which the heart was still in fairly good condition, the injection of epinephrin produced a sudden complete paralysis. We have seen a similar effect in a heart weakened by chloral. Epinephrin, in other words, by causing a great rise in blood pressure may overwhelm a weakened heart.

In mammals, cats and dogs, there is evidence of some cerebral depression as is shown by the greater quiet of the animal. The

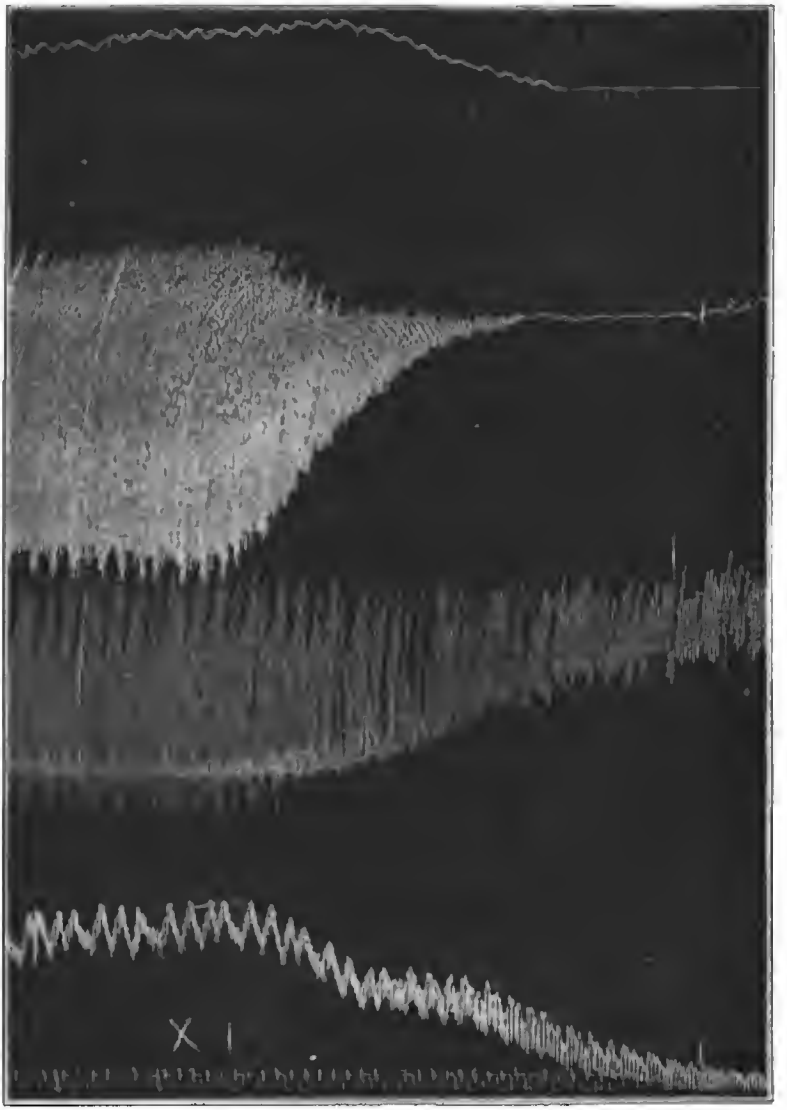

FIG. 4.—Record of kidney volume, auricular contractions, ventricular contractions, and carotid blood-pressure in dog. In the cardiac tracing the upstroke is diastolic, the down stroke systolic. At *X*, 40 mgs. emetin hydrochloride injected intravenously.

doses which induce this, however, cause nausea or vomiting, and the depression may be looked on as an accompaniment of these

effects. Only with doses which approach lethal ones, does the depression become marked and out of proportion to the emetic effect.

In connection with the action on the central nervous system the effect on respiration is of interest. According to Kunkel[17] the respiration is effected before cardiac weakness develops, and respiratory stoppage occurs before cardiac paralysis. This statement should be modified somewhat. With subcutaneous injections respiration stops before the heart. The latter shows depression early, however, and when the respirations stop the blood-pressure is very considerably lowered and the heart contractions weakened. Artificial respiration at this stage fails to bring about a circulatory recovery, although the circulation may continue, at a low level, for a considerable time. With intravenous injections, coincident with the fall in blood-pressure, the respiratory movements increase in rate or volume (Fig. 2) and continue for some time after the heart has stopped beating and the blood-pressure fallen to zero. The respiratory changes in this instance may be considered as dependent on circulatory failure.

In short experiments emetin has little influence on the kidney as far as diuresis is concerned. During the fall in blood-pressure a diminution or stoppage in urine flow occurs, as would naturally be expected. Otherwise no changes are noticed. In dogs given daily injections of emetin the amount of urine passed increases on each succeeding day and may finally reach two or three times the normal output. The urine contains small quantities of albumin, but gives no evidence of severe damage to the kidney. The effect on urine output is such as may occur from any mild irritation, and post-mortem examination of the kidney shows that this is the only morphological change usually seen.

A few experiments have been made on the uterus. The uteri of virgin guinea-pigs and of those in early pregnancy were used, being suspended in an oxygenated Locke solution, according to the method of Dale.[18] On adding emetin to the fluid no change in uterine movement was obtained excepting a slight increase in tonicity, as evidenced by a shortening of the muscle. The effect is quite distinct from that obtained by adding such drugs as ergot or pituitary extract.

The only study of metabolism in animals given emetin is that made by Meyer and Williams. We have carried this work further in so far as nitrogen metabolism is concerned. The experiments were carried out on fasting dogs, and the urine collected in 24-hour periods. The total nitrogen was estimated by the Kjehldal method, the urea and ammonia by the Van Slyke and Folin methods respectively. There is seen an increase in the total nitrogen, urea nitrogen,

[17] Handbuch der Toxikol., 1901, p. 843.

[18] Dale and Laidlaw, Jour. Pharmacol. and Exper. Therap., 1912, iv, 75.

and ammonia nitrogen following the emetin administration (see Table). This increase in nitrogenous metabolism is in accord with

DOG No. XVI.

Day.	Urine in 24 hrs.	Sp. Gr.	Total "N."	Urea "N."	NH_3 "N."
	C.c.		Gm.	Gm.	Gm.
Oct. 27	120	1.040	3.59	2.42	0.210
Oct. 28	70	1.062	3.36	1.17	0.140
Oct. 29	59	1.060	2.89	1.94	0.165
11.30 A.M. Injected 2.5 c.c. emetin (1 per cent. solution).					
Oct. 30	80	1.070	3.87	2.82	0.222
10.15 A.M. Injected 2.5 c.c. emetin.					
Oct. 31	120	1.065	5.25	4.30	0.319
Nov. 1	155	1.052	5.05	4.24	0.293
Nov. 2	150	1.034	3.95	3.65	0.277
11.00 A.M. Injected 2.5 c.c. emetin.					
Nov. 3	315	1.030	5.64	3.21	0.389

DOG No. XVII.

Nov. 9	60	1.060	3.06	2.37	0.217
Nov. 10	65	1.050	3.30	2.71	0.143
Nov. 11	65	1.050	3.43	2.68	0.448
Nov. 12	65	1.050	3.05	2.69	0.126
Nov. 13	75	1.060	3.28	2.87	0.105
Injected 3 c.c. emetin (1 per cent. solution).					
Nov. 14	100	1.070	4.70	4.42	0.140
Injected 3 c.c. emetin solution.					
Nov. 15	175	..	6.16	5.49	0.299

the results of Meyer and Williams. Similar changes are induced by arsenic, phosphorous, potassium cyanide, and other poisons and are commonly explained as results of interference with intracellular metabolism with an accompanying acidosis.

Finally in an attempt to explain the former wide-spread use of emetin in checking hemorrhage, we have determined, by means of Wright's coagulometer, whether the coagulability of the blood is influenced by the drug. The subcutaneous injection of a good sized dose of emetin into a cat fails to affect the coagulation time to any appreciable degree. Since then there is no action on the lungs, blood, bloodvessels, or uterus, which would account for a hemostatic effect, we are forced to assume that such an effect, if present, is due to the general relaxation which is an accompaniment to the action of emetics given in too small doses to induce vomiting. As a matter of fact we have noticed a fluidity of the blood on autopsy.

We have not attempted to study the action of emetin on the ameba. Its specificity in this connection seems no longer open to question. Vedder[19] had shown, conclusively, that emetin is strongly amebacidal to all forms of non-pathogenic ameba in the dilution of 1 to 100,000. Rogers[20] demonstrated that an equal toxicity

[19] Vedder, Bull. Manila Med. Soc., 1911, iii, 48; Jour. Am. Med. Assn., 1914, lxii, 501.

[20] Rogers, loc. cit.

is shown against pathogenic forms. Weaker solutions while not so strongly amebacidal, exercise a definitely deleterious action on the parasite. To obtain a 1 to 100,000 solution in the blood it would be necessary to have about 0.05 gm. of emetin in the circulation at one time. As the dose given is generally smaller than this, and it is not completely taken up into the blood stream from the point of injection for some hours, it is evident that the dilution is considerably greater than this figure. It seems safe to assume, however, that emetin is excreted along the whole alimentary tract. In this case its longer stay in the excretory tissues, or the greater concentration in which it may exist during excretion, would account for a sufficiently strong amebacidal action.

Contrary to the statement of Lowin we have found, on patients, that emetin usually produces a definite local irritation after a subcutaneous or intramuscular injection. There is some redness, pain, swelling and occasionally edema in the part, most marked for the first two or three days, and gradually subsiding in about a week. If applied to mucous membranes there appear small pin-head-sized vesicles which rupture, leaving small ulcers. These, however, rapidly disappear. These effects are undoubtedly well known to all who have been using emetin in the treatment of pyorrhea alveolaris.

SUMMARY. From our experiments we wish to emphasize the following points:

1. Emetin depresses and may eventually paralyze the heart.
2. It is a powerful gastro-intestinal irritant whether given by mouth or subcutaneous injection.
3. It causes a definite derangement of metabolism, characterized by an increase in nitrogen loss and an acidosis.
4. While in normal individuals given moderate doses, these actions may not be of importance, in pathological states of the circulation, intestinal tract, or metabolism, they may be a very definite source of danger.

EFFECTS OF RETENTION IN THE KIDNEY OF MEDIA EMPLOYED IN PYELOGRAPHY.

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WITH the recognition of the diagnostic value of pyelography came the realization that the method was not without danger to the patient. Deaths were reported by various observers, which